WILEY ENCYCLOPEDIA OF

MOLECULAR MEDICINE

Reprints from Wiley Encyclopedia of Molecular Medicine, 5 Vol. Set
ISBN 0-471-37494-6

CONCLUSION

The term "bifunctional enzyme" has been used somewhat ambiguously in reference to two multifunctional proteins that are integral to peroxisomal β-oxidation of fatty acids. MFP1 has enoyl-CoA hydratase, L-hydroxyacyl-CoA dehydrogenase, and enoyl-CoA isomerase activities. MFP2 has enoyl-CoA hydratase and D-hydroxyacyl-CoA dehydrogenase, and in addition has a sterol carrier protein 2-like domain. Although MFP1 is required for the peroxisomal degradation of straight-chain fatty acids, oxidation of branched-chain fatty acids and the synthesis of bile acids from cholesterol requires MFP2. Human disease resulting from a deficiency of MFP2 is now well characterized, and all cases of "bifunctional enzyme" deficiency are thought to be caused by mutations in the gene for MFP2 and not MFP1. However, these patients have impaired β-oxidation of very long-chain fatty acids, which presumably proceeds via the L-specific MFP1, as well as branched-chain fatty acids. Thus, there are interactions between the enzymes of the D- and L-specific pathways that remain poorly understood.

GENBANK ACCESSION NUMBERS

NP 001957 human MFP1
AF057740 human MFP2

BIBLIOGRAPHY

1. M. Dieuaide-Noubhani et al., *Eur. J. Biochem.* **240**, 660–666 (1996).
2. M. Dieuaide-Noubhani et al., *Biochem. J.* **321**, 253–259 (1997).
3. U. Seedorf et al., *J. Biol. Chem.* **269**, 21277–21283 (1994).
4. V.D. Antonenkov et al., *J. Biol. Chem.* **272**, 26023–26031 (1997).
5. L.L. Jiang et al., *J. Biochem. (Tokyo)* **120**, 624–632 (1996).
6. S. Naidu et al., *Neurology* **38**, 1100–1107 (1988).
7. M.R. Natowicz et al., *Am. J. Med. Genet.* **63**, 356–362 (1996).
8. P.A. Watkins et al., *J. Clin. Invest.* **83**, 771–777 (1989).
9. E.G. van Grunsven et al., *Am. J. Hum. Genet.* **64**, 99–107 (1999).
10. E.G. van Grunsven et al., *Proc. Natl. Acad. Sci. U.S.A.* **95**, 2128–2133 (1998).

ADDITIONAL READING

Adamski J. et al., Steroids, fatty acyl-CoA, and sterols are substrates of 80-kDa multifunctional protein, *Steroids* **62**, 159–163 (1997).

Hashimoto T., Peroxisomal beta-oxidation enzymes, *Neurochem. Res.* **24**, 551–563 (1999).

Kunau W.H., Dommes V., and Schulz H., β-oxidation of fatty acids in mitochondria, peroxisomes, and bacteria: a century of continued progress, *Prog. Lipid Res.* **34**, 267–342 (1995).

Lazarow P.B. and Moser H.W., Disorders of Peroxisome Biogenesis, in C.R. Scriver, A.L. Beaudet, W.S. Sly and D. Valle, eds., *The Metabolic and Molecular Basis of Inherited Disease*, McGraw-Hill, New York, 1995, pp. 2287–2324.

Wanders R.J. and Tager J.M., Lipid metabolism in peroxisomes in relation to human disease, *Mol. Aspects Med.* **19**, 69–154 (1998).

Watkins P.A. et al., Distinction between peroxisomal bifunctional enzyme and Acyl-CoA oxidase deficiencies, *Ann. Neurol.* **38**, 472–477 (1995).

BIGLYCAN

MARIAN F. YOUNG
X.-D. CHEN
National Institute of Dental and Craniofacial Research
Bethesda, Maryland

Biglycan (*BGN*) is a member of a family of small proteoglycans known as *SLRPs* (small leucine rich proteoglycans) whose members are composed of repeating units of a leucine-rich repeat (LRR). The core protein of biglycan is approximately 40 kD and has, as its name implies, two glycosaminoglycan (GAG) chains attached near its amino terminus. The composition of the GAG chains can be either dermatan sulfate (DS) or chondroitin sulfate (CS) depending on the tissue source. Biglycan has been reported to bind to other matrix proteins, including TGF-β and type I collagen, and is closely related to the SLRP known as decorin. It is expressed in numerous specialized tissues such as bone, cartilage, and muscle and often assumes a "pericellular" location implying a role in cell function. The human biglycan gene has 7 introns and 8 exons and is located on the tip of the X chromosome (Xq27-ter). The gene is regulated by numerous growth factors and hormones including TGF-β, retinoic acid, and dexamethasone in a manner that is tissue-specific. Although no genetic mutations have been ascribed to the biglycan gene till date, numerous genetic and acquired diseases have implicated biglycan dysregulation including Turner's syndrome, Ehlers-Danlos syndrome, muscular dystrophy, and osteoporosis.

PROTEIN STRUCTURE AND FUNCTION

Biglycan was first characterized by biochemical purification from bone and shown to be a proteoglycan heterogenous in molecular weight that contained chondrointin-4 sulfate (1). Antibodies from synthetic peptides were used to isolate a full-length cDNA from an expression library and the entire structure determined by DNA sequencing (GenBank/EMBL accession # NM_001711) (2) (Fig. 1). The deduced protein sequence predicts that biglycan has a hydrophobic leader sequence for secretion (prepeptide) followed by a propeptide which is retained or differentially cleaved in certain tissues (3). Two characteristic cysteine clusters flank a series of tandem repeats that are nominally 24 amino acids long and contain a leucine rich sequence (LRR) with the consensus LxxLxLxxNxLx. Figure 1 illustrates that the LRR repeats make up almost all of the biglycan core protein. The protein has

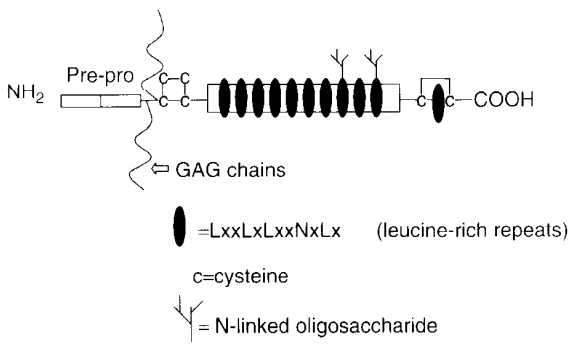

Figure 1. Diagram of the key structural features in human biglycan.

two GAG chains attached near the NH_2 terminus and therefore was given the name biglycan. In bone the GAG chains are CS and in soft tissues, they are generally DS.

Biglycan has been shown to bind TGF-β (4) and is implicated to regulate its activities. On the basis of this binding property there is speculation that biglycan could attenuate fibrosis by absorbing free TGF-β and making it unavailable for stimulating further matrix accumulation (5). There is some controversy about whether biglycan directly binds to type I collagen (6); however, recent work using mice deficient in biglycan shows that collagen fibrils are larger and more irregular than normal controls (7), indicating a role (though possibly indirect) in collagen fibril assembly in vivo.

GENE STRUCTURE, EXPRESSION, AND REGULATION

Using somatic cell hybrids, biglycan (*BGN*) was broadly mapped to the X chromosome (8). Fine mapping using in situ hybridization showed its precise location to be Xq27-ter. The gene is approximately 8 kilobases (kb) long and composed of seven introns and eight exons (GenBank/EMBL accession # AH002674) (9). The exons do not appear to encode discrete protein domains but, interestingly, are completely identical in length and position to the decorin gene. This observation supports the speculation that the genes arose from a gene duplication event some time during evolution and that the proteins may share some functional properties. In this regard it is noted that both biglycan and decorin bind TGF-β and type I collagen and are implicated in regulating their activities (10,11). Comprehensive analysis of the tissue location of biglycan shows that it is expressed in numerous specialized connective tissues such as bone, cartilage, muscle, and the keratinocyte layer of the skin. In many tissues it assumes a "pericellular" arrangement. Decorin is often found in the same tissues as biglycan but shows clear differences in localization, being relatively more abundant in the "interterritorial" matrix (3). For example, in the developing small bones of the hand, biglycan expression is prominent in the articular cartilage "cap," whereas decorin is located more internally in the deep, cartilaginous resting zone (12). The factors that control the expression of biglycan are not entirely known but several factors influence its expression in vitro including dexamethasone, retinoic acid, and TGF-β (10,11). The human biglycan promoter contains a GC (guanine cytosine)-rich area that binds a transcription factor cKROX (13). Independent studies using the human gene indicated that it is controlled by cAMP through signaling pathways involving protein kinase A and the transcription factors SP1/SP3 (14).

BIGLYCAN AND DISEASE

The localization of biglycan to skeletal tissues coupled with the fact that it resides on the X chromosome led researchers to examine regulation in patients with Turner's Syndrome, a disease characterized by its short stature and early-onset osteoporosis. mRNA and protein analysis for biglycan in cells obtained from Turner's (45, X0) as well as from patients with additional X or Y chromosomes (Kleinfelter's syndrome) showed a clear proportional relationship between the number of X (or Y) chromosomes and biglycan expression (15). Previous studies showed that one copy of the biglycan is inactivated during development. Taken together, a theory was proposed that a second gene found on both Y and a portion of X that escapes inactivation might control the biglycan gene and contribute to its unique "pseudoautosomal" expression pattern (15).

Transgenic mice lacking biglycan (knockout, KO) acquire a phenotype resembling osteoporosis (16). Specifically biglycan KO mice develop age-related osteopenia and achieve a lower "peak bone mass" compared to normal littermates. Further studies showed that the mice have impaired bone formation because of a defect in the quantity of the bone cell precursors called *marrow stromal cells* (MSC) and in their ability to form bone (17). In muscle biglycan was shown to bind to α-dystroglcyan, an integral component of the dystrophin-associated complex (DAPC) that links the cytoskeleton to the extracellular matrix (ECM) (18). The upregulation of biglycan in mice with muscular dystrophy (mdx) further implicates a role for biglycan in the pathogenesis of this disease (18). A patient with a progeroid variant of Ehlers-Danlos was described with a defective galactosyl transferase I, an enzyme essential for glycosaminoglycan synthesis onto both biglycan and decorin (19). The patient had generalized osteopenia and loose, elastic skin. In this regard it is interesting to note that mice deficient in both decorin and biglycan have a similar phenotype (ie., fragile skin and osteopenic bone), suggesting that GAG attachment may be critical to biglycan (and decorin) function in affected tissues (7). In summary biglycan is a leucine-rich small proteoglycan with numerous potential functions at tissue, cell, and molecular levels (10,11,20,21).

BIBLIOGRAPHY

1. L.M Fisher et al., *J. Biol. Chem.* **258**(10), 6588–6594 (1983).
2. L.W. Fisher, J.D. Termine, and M.F. Young, *J. Biol. Chem.* **264**(8), 4571–4576 (1989).
3. P. Bianco, M. Riminucci, and L.W. Fisher, in J.E. Scott, ed., *Dermatan Sulfate Proteoglycans; Chemistry, Biology, Chemical Pathology*, Portland Press, London, 1993, pp. 193–205.
4. A. Hildebrand et al., *Biochem. J.* **302**, 527–534 (1994).
5. W.A. Border et al., *Nature* **360**(6402), 361–364 (1992).
6. E. Schonherr et al., *J. Biol. Chem.* **270**, 8877–8883 (1995).
7. A. Corsi et al., *J. Bone. Miner. Res.* **14**(Suppl. 1), S134 (1994).
8. O.W. McBride, L.W. Fisher, and M.F. Young, *Genomics* **6**(2), 219–25 (1990).
9. L.W. Fisher et al., *J. Biol. Chem.* **266**(22), 14371–14377 (1991).
10. A.M. Hocking, T. Shinomura, and D.J. McQuillan, *Matrix Biol.* **17**, 1–19 (1998).
11. R.V. Iozzo, *J. Biol. Chem.* **274**(27), 18843–18846 (1999).
12. P. Bianco et al., *J. Histochem. Cytochem.* **38**(11), 1549–1563 (1990).
13. A.M. Heegaard et al., *J. Bone Miner. Res.* **12**(12), 2050–2060 (1997).
14. H. Ungefroren, B. Gellersen, N.B. Krull, and H. Kalthoff, *J Biol. Chem.* **273**(44), 29230–29240 (1998).
15. C. Geerkens et al., *Hum. Genet.* **96**(1), 44–52 (1995).
16. S. Xu et al., *Nat. Genet.* **20**, 78–82 (1998).
17. X.-D. Chen, T. Xu, and M.F. Young, *J. Bone Miner. Res.* **14**(Suppl. 1), S133 (1999).
18. M.A. Bowe, D.B. Mendis, and J.R. Fallon, *J. Cell Biol.* **148**(4), 801–810 (2000).
19. H. Kresse et al., *Am. J. Hum. Genet.* **41**, 436–453 (1987).
20. R.V. Lozzo and A.D. Murdoch *Faseb J.* **10**(5), 598–614 (1996).
21. R.V. Lozzo, *Annu. Rev. Biochem.* **67**, 609–652 (1998).